Boehringer Ingelheim

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Boehringer Ingelheim
Pharmaceuticals Inc.

November 29, 1999

Re: Docket Number 97N-0023
Proposed Rule: ***Use of Ozone Depleting Substances; Essential Use Determinations.***

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Dear Madam and/or Sir,

In response to the above referenced Federal *Register* notice of September 1, 1999 (64 FR 47719), Boehringer Ingelheim Pharmaceuticals, Inc. is pleased to submit the attached comments for consideration by the Food and Drug Administration.

Should you have any questions regarding this submission or require additional information, my contact information appears to the right.

Sincerely,

Joseph M. Ferrara
Director, Government Policy

97N-0023

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Comments by Boehringer Ingelheim Pharmaceuticals, Inc.

OU

Proposed Rule:
Use of Ozone Depleting Substances; Essential Use Determinations

Federal Register, September 1, 1999 (64 FR 47719)
Docket No. 97N-0023

November 29, 1999

INTRODUCTION

Boehringer Ingelheim Pharmaceuticals, Inc (Boehringer Ingelheim) is providing these comments in response to the request of the Food and Drug Administration (FDA) in the above captioned Proposed Rule.

Boehringer Ingelheim is committed to improving respiratory care through the development of safe, effective and environmentally responsible therapies. For almost forty years Boehringer Ingelheim has been a world leader in the research, development, and manufacture of drug products for the management of respiratory disease. Over eight million patients worldwide with chronic obstructive pulmonary disease (COPD) and asthma rely on medications from Boehringer Ingelheim. Recognizing that an individual patient may need a particular type of drug delivery system, the company has developed a variety of products that include Metered Dose Inhalers (MDIs), Dry Powder Inhalers (DPIs), and solutions for nebulization. The company is actively involved in the development of new drugs and new delivery systems to benefit patients, physicians and the environment alike.

In the United States, Boehringer Ingelheim has introduced many effective products for the treatment of COPD and asthma, including ALUPENT® (metaproterenol sulfate), ATROVENT® (ipratropium bromide), and COMBIVENT® (ipratropium bromide and albuterol sulfate) Inhalation Aerosols. These drug products contain chlorofluorocarbons (CFCs) and would be affected by the above referenced Proposed Rule. (Noting the proposal in 21CFR § 2.125(a) to use the term ozone-depleting substance instead of chlorofluorocarbon, all further references in these comments will be to the former term or its acronym, ODS)

Protection of the environment and public health form an integral part of future planning at Boehringer Ingelheim, which is dedicated to the research and development of non-ODS alternatives in respiratory products. Boehringer Ingelheim is fully committed to the phase-out of ODS propellants. The company has invested more than $270 million dollars in the development of hydrofluoroalkane (HFA) propellant based MDIs and the

development of a unique propellant-free system – RESPIMAT® Soft Mist Inhaler. This extensive research and development program involving 10,000 patients in clinical trials is further demonstration that Boehringer Ingelheim is taking a leading role in the global transition from ODS to non-ODS devices.

Boehringer Ingelheim commends the FDA on its efforts to develop this Proposed Rule. We recognize the value of amending 21 CFR §2.125 concerning the use of ODS in self-pressurized containers to make it consistent with other laws. Boehringer Ingelheim also appreciates the opportunity to provide the following comments to the Agency and thereby share the company's extensive clinical trial and post-marketing experience that bears directly on the issues raised in this Proposed Rule. We hope that through our comments we may assist the Agency in developing a Final Rule that will benefit patients, physicians and the environment alike.

A number of the comments Boehtinger Ingelheim is providing concerning this Proposed Rule are consistent with the comments the company submitted on May 2, 1997 (Docket No. 97N-0023) concerning the March 6, 1997 Advanced Notice of Proposed Rulemaking. A copy of the May 2, 1997 submission is attached.

GENERAL APPROACH FOR DEVELOPMENT OF POLICY

The FDA should be an active player in the global decision to phase out ODS containing products. Manufacturers of inhalers should have an incentive to develop alternatives and patients and health care providers should have a clear understanding about the limited period of time that ODS containing inhalers will be available. The proposed rule should meet at least those two goals. While Boehringer Ingelheim believes that the majority of provisions in the proposed rule are consistent with these goals, it believes that others are inconsistent with those goals. Our comments focus on those few provisions with which we have some concerns or which we believe need clarification or emphasis. A list of provisions, which we support without reservation, conclude our comments.

ISSUES OF CONCERN OR REQUIRING CLARIFICATION

Grandfathering essentiality for new ODS containing products containing active moieties on the current essential use list

In section III.B. 11. Specific Comment on the ANPRM Number 80, it is stated that FDA will not withhold approval for a drug product that contains a moiety listed as an essential use under 2.125(e).

As mentioned in our comments to the March 6, 1997 ANPRM, Boehringer Ingelheim joined with several speakers at the April 11, 1997 Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting in recommending an immediate halt to the approval of new ODS-MDIs except for a new medication that meets an unmet therapeutic need. While we recognize that it is difficult for FDA to decline

to approve a safe and effective product, we note that deeming that a new product is eligible for an essential use is not governed exclusively by the Food Drug and Cosmetic Act (FDCA). In addition to the FDCA, the Clean Air Act and several international treaties including the Montreal Protocol govern essential use determinations. The continued deeming of essentiality of ODS-MDIs except in the cases where there is an unmet therapeutic need is against the spirit of the Montreal Protocol and the direction of this Proposed Rule. **The use of an ODS in a new product should not be presumed to be essential solely because it contains an active moiety that is in an ODS product on the current essential use list.**

Continuing to deem essential ODS-containing MDIs simply because they contain the same active moiety that is in an ODS product on the current essential use list sends a misleading message to patients and their physicians that the transition to non-ODS inhalers is a remote possibility rather than an imminent certainty. That message will act to discourage both patients and physicians to plan for a switch to non-ODS alternative products. In its April 1998 and 1999 reports the Technology and Economic Assessment Panel (TEAP) of the Parties to the Montreal Protocol (Parties), noted that continued approval of new ODS–containing MDIs is likely to discourage reformulation efforts and impede the MDI transition. It would also raise doubts in the minds of physicians and patients about whether a change in medications will actually be required. Finally, continued approval of ODS-MDIs will increase health risks for patients who may have to switch medications twice – first to a newly approved ODS-containing MDI and then to an ODS-free MDI.

It is critical that all parties, including the FDA, consider and work toward minimizing any patient confusion associated with the transition process. Every time a patient switches from one product to another, the potential for an increase in the frequency of adverse events or product complaints is increased because of differences between the old and new products. These adverse events have the effect of reducing patient compliance in using the product. While a certain number of adverse events are inevitable when large populations of patients are making a switch from one product to another, there is no reason to permit the possible doubling of the number of those events by allowing the introduction of new ODS containing products. Patients will have to switch once. There is no legitimate reason to establish a regulatory policy that will result in their switching more than once.

To automatically deem essential the use of additional ODS products because they contain the same active moiety that is in an ODS product currently on the essential use list is inconsistent with the provisions of this Proposed Rule regarding the addition of new essential uses (§2.125(f)). In section 11.1. Petitions to Add New Essential Uses, FDA states

> *"...it would be inappropriate to add new essential uses to §2.125 in all but the most extraordinary circumstances because of the relatively near-term phase-out of the production and importation of ODSs."*

FDA proposes a requirement of "compelling evidence" in support of a petition for a new essential use. This compelling evidence includes a demonstration that substantial technical barriers exist to formulating the product without ODSs and that the product will provide an unavailable public health benefit. Boehringer Ingelheim believes these provisions establish an appropriate burden of proof on the party petitioning for a new essential use in light of the mandate of the Montreal Protocol for the worldwide phase-out of ODSs and the MDI transition.

Boehtinger Ingelheim believes that FDA should apply the same requirements to a new ODS-MD1 product containing, the same active moiety that is in an ODS product on the current essential use list. The active moieties in virtually all of the products currently on the essential use list are being actively reformulated to non-ODS alternatives. Based on this, additional ODS-MDIs containing the same active moieties would not meet the requirement for "compelling evidence" of either technical barriers (alternatives are being developed) or an unavailable public health benefit (active moieties are currently available). Therefore, there is no need for additional ODS-MDIs containing the same active moiety that is in an ODS product on the current essential use list,

Boehringer Ingelheim believes that FDA should not grant essentiality for any ODS product, unless it meets the provisions of proposed §2.125(f).

Consideration of cost

In section 11.1.3, Evidence to Support New Essential Uses for Investigational and Noninvestigational Products, FDA proposes to consider cost as a technical barrier for determining if a non-ODS product can be considered an alternative to an ODS product currently on the essential use list.

In section II.K, Determinations of Continued Essentiality, FDA proposes to consider whether a high-priced non-ODS product is effectively unavailable to a portion of the patient population because they cannot afford to buy the product.

In section III.B.13, Specific Comment on the ANPRM Number 97, FDA proposes to consider cost in determining whether alternatives meet patient needs,

Boehringer Ingelheim strenuously opposes the inclusion of cost as a criterion that FDA may use in evaluating whether non-ODS products are acceptable as alternatives to ODS products.

Current law authorizes FDA to evaluate the safety and efficacy of new chemical entities as pharmaceutical products and to determine the equivalency of generic products. No provision in the Food, Drug and Cosmetic Act authorizes the FDA to evaluate the cost of pharmaceutical products.

The additional burden of evaluating cost is not a simple task. Evaluating cost does not simply involve comparing prices. Evaluating the cost of a product may require the consideration of whether use of a less expensive product will diminish the rate of patient compliance. The methodology for deriving cost comparisons is complex, including but not limited to decision, Markov and state-transition models. The level of expertise and resources necessary to conduct cost analyses is significant and, we believe currently not available at FDA.

Additionally, precise criteria that FDA might follow are lacking in the Proposed Rule. Although the preamble includes reference to the terms, the text of the proposed rule does not define what constitutes a 'prohibitively high' price or what constitutes a 'portion' of the population. Similarly, FDA has no expertise in predicting how public and private health insurance will deal with any changes in prices charged for non-ODS products.

One of the major goals of the Montreal Protocol is the complete removal of ODSs from all products. Requiring cost analyses before an ODS containing product could be removed could substantially delay meeting that goal. In addition, that delay will significantly erode the incentive for manufacturers to innovate and develop alternative therapies. The FDA is aware that manufacturers have spent many years developing alternative products. The process has proven to be extremely challenging. There is no reason that FDA should make the transition process even more challenging by establishing an unprecedented regulatory step that must be met before an ODS product may be removed.

Boehringer Ingelheim believes it inappropriate to include economic considerations in an assessment of scientific evidence for the acceptability of alternative products. This belief was echoed by the PADAC which met on November 22, 1999, and after lengthy discussion, was unable to reach a consensus about how economic factors could be used in reviewing the acceptability of alternative products. FDA has steadfastly maintained that it never takes economic considerations into account when it approves products. The agency should not begin that practice now. Boehringer Ingelheim believes that allowing a regulatory body to make approval decisions on the basis of cost will distort the market incentives that permit the development of more effective and safer products. A proposal such as this would set a dangerous precedent that could threaten the economic foundation of the pharmaceutical industry.

Reauirement to exercise due diligence in reformulating products

In section III.B.8, Specific Comment on the ANPRM Number 52, it is stated that "FDA expects that under the moiety-by-moiety approach in this proposal companies will not lose essential use exemptions prior to approval of an alternative product if they are exercising due diligence in reformulating their products."

Boehringer Ingelheim agrees with FDA that companies exercising due diligence in reformulating their ODS-MDIs should not lose essential use exemptions prior

to approval of an alternative product. Boehtinger Ingelheim notes that the TEAP recommended in its April 1999 report that the Parties should verify whether manufacturers are actively pursuing research and development efforts or actively entering into licensing arrangements on non-ODS alternatives.

Boehringer Ingelheim recommends that FDA require those firms that are either seeking new essential use designations or want to retain existing essential use designations to show that they are actively pursuing reformulation to a non-ODS alternative as a criteria for essential use designation.

Availability of multiple alternatives prior to removal of essential use designation

In section II.K, Determination of Continued Essentiality, it is explained that in the case of active moieties represented by more than one new drug application (NDA) or by more than one strength, the Proposed Rule would require at least two acceptable non-ODS alternative products that contain the same active moiety to be marketed before FDA would consider removing the essential use designation for that active moiety (proposed §2.125(g)(4)).

Elsewhere in the preamble this requirement is described in somewhat inconsistent terms. For instance, in section II.A.2, FDA uses the term "multiple products" rather than "two or more NDAs." Additionally in section III.B. 13, Response Number 97, FDA uses the term "multiple-source" ODS-MDIs. These two terms are not synonymous with "two or more NDAs." We recommend that these inconsistencies be removed when the final rule is published and that the term "two or more NDAs" in section II.K be the only explanation of §2.125(g)(4).

Boehringer Ingelheim agrees with FDA, that ODS products of the same active moiety marketed in distinct strengths will need to be replaced by distinct strengths of non-ODS products of the same active moiety.

Boehringer Ingelheim also supports this provision with regard to the replacement of an ODS-MD1 with a non-ODS multiple-dose DPI (MDPI). As mentioned in our comments to the March 6, 1997 ANPRM, we believe that a MDPI alone is not an appropriate alternative as these devices require, by design, patient effort to deliver the drug. For example, DPIs require a patient's inspiratory flow rate (IFR) to be sufficient to evacuate powder from the device. A subgroup of severe, COPD patients may not be able to generate an adequate IFR to optimize drug delivery from a MDPI. Clearly, a MDPI would not be an appropriate single, non-ODS alternative.

Boehringer Ingelheim supports proposed §2.125(g)(4) requiring more than one alternative product to be available for each active moiety only when that active moiety is represented by two or more NDAs.

Removal of essentiality designation despite unavailability of alternatives

The Proposed Rule provides for notice and comment rulemaking to designate an ODS-MDI nonessential under proposed 92.125(f) after 1 January 2005, even if no alternative to that ODS-MD1 has become available (proposed §2.125(g)(2)).

Boehringer Ingelheim agrees with the FDA's statement in section II.K, Determination of Continued Essentiality, that "even if all current essential use moieties are not reformulated, sufficient alternative products may exist in the future to fully meet the needs of patients." Boehringer Ingelheim also supports FDA's intent to consult with an advisory committee and provide the opportunity for public comment before making such a determination.

Boehringer Ingelheim recommends that FDA undertake an evaluation of those ODS-MD1 products remaining on the market after January 1, 2005 to ensure that these products remain necessary to meet the needs of patients at that time.

Demonstration of adeauate production capacity

The Proposed Rule requires that supplies and production capacity for the non-ODS product must ". . . . exist or will exist at levels sufficient to meet patient need" (proposed §2.125(g)(3)(ii)). In section II.K, Determination of Continued Essentiality, the expectation stated is that ". . . .the non-ODS product will be manufactured at multiple manufacturing sites if the ODS product was manufactured at multiple manufacturing sites."

Boehringer Ingelheim believes that to ensure that patient health will be protected during the transition, supplies and production capacity of the non-ODS alternative must exist or will exist at levels sufficient to meet patient need. If a manufacturer of a non-ODS alternative product can demonstrate that a single site will be sufficient to meet patient needs, however, then multiple manufacturing sites should not be necessary. There may be no correlation between the number of sites necessary to provide ODS products and the number necessary to provide non-ODS products. For example, the new site manufacturing non-ODS products may be larger or have a greater production capacity than the sites making ODS products.

Boehringer Ingelheim, therefore, recommends that FDA allow manufacturers of non-ODS alternatives to demonstrate their ability to meet patient needs through a single manufacturing site before requiring multiple manufacturing sites.

Expedited Review of non-ODS Products

In section III.B. 12, (Specific Comment on the ANPRM Number 79), FDA indicates that it does not believe that NDAs for ODS replacement products meet the criteria for priority review.

Boehringer Ingelheim notes that, at the PADAC meeting of April 11, 1997, FDA asked the Committee for recommendations on incentives that could be used to stimulate manufacturers to accelerate development of non-ODS products. The unanimous response from Committee members and public alike was to accelerate the reviews of NDAs for alternative products. Boehringer Ingelheim agrees that the review of NDAs for ODS-MD1 alternatives should be accelerated. This is consistent with the decision of the parties to the Montreal Protocol, urging parties to request their national authorities to expedite review of marketing applications for ODS-MD1 alternative products.

Boehringer Ingelheim also notes that in the Specific Comment on the ANPRM Number 79 cited above, FDA states

The agency is committed to the timely review of all drug applications."

Boehringer Ingelheim requests the Agency give additional consideration to our previous request for "priority review" and consider implementation of appropriate procedures and policies to facilitate the review of NDAs for non-ODS replacement products. As a basis for this request, we refer to FDA's longstanding policy for the review priority classification of NDAs, as described in the CDER MAPP 6020.3 Priority Review Policy. This MAPP states that a priority review should be given to those drug products which, if approved, "would be a **significant improvement** compared to marketed products in the treatment, diagnosis, or prevention of a disease". It is our contention that non-ODS replacement products meet this criterion for priority review, based on interpretation of the stated requirement for "significant improvement compared to marketed products".

As per the examples given in MAPP 6020.3, a significant improvement could be demonstrated by improved effectiveness or safety of the drug product for the patient. These examples relate the concept of "significant improvement" to direct patient benefit. However, a significant improvement could equally well be measured in terms of the benefit to the environment, and resulting public health benefit.

The provisional continued use of ODSs only in "essential use" drug products is *de facto* recognition of the importance of the adverse environmental impact of ODS, *i.e.*, only in exceptional cases should ODSs continue to be used in drug products. It therefore is consistent that a priority review classification should be assigned to ODS-replacement

products, based on the importance of the resulting improvement to the environment and public health.

Boehringer Ingelheim requests that FDA interpret its existing policy MAPP 6020.3 accordingly for priority review designation of ODS-replacement NDAs.

We believe that a more specific commitment is needed, and ask that the Agency consider the following reasons and concerns:

- Some form of rapid review process was supported by the Advisory Committee and was requested in fourteen (14) comments to the ANPR.

- As published on FDA's Internet site, the time elapsed between submission and approval of NDAs for new pulmonary drug products has been as much as 68 months.

- Non-ODS products were developed by the pharmaceutical industry as a good faith effort to comply with the provisions of the Montreal Protocol.

- Pharmaceutical-quality ODS supplies from stockpiles and new production are expected to decline in the next few years as MDIs are the only exempt use.

- Industry and government have a public health mandate to ensure the supply of medication for millions of asthma and COPD patients.

- Replacement products do not introduce new drug substances.

- Extensive patient use data may be available from the use of approved non-ODS products in other countries.

PROPOSALS SUPPORTED

On the basis of the regulatory text and the explanatory material contained in the preamble, Boehringer Ingelheim supports the provisions in the proposed rule that

- require a moiety-by-moiety substitution before removal of an essentiality designation (proposed §2.125(g)(3)(i) and (g)(4)(i));

- list separately each individual moiety deemed an essential use (proposed §2.125(e)).

- change the designation of ODS products not listed in 92.125(e) from adulterated and misbranded to nonessential

- provide that an alternative to an ODS-MD1 is acceptable only if it is "marketed for the same route of administration" as the product it is replacing (proposed §2.125(g)(3)(i) and (g)(4)(i));

- provide that an alternative to an ODS-MDI is acceptable only if it is "for the same indication" as the product it is replacing ('proposed §2.125(g)(3)(i) and (g)(4)(i));

- provide that an alternative to an ODS-MD1 is acceptable only if it has "approximately the same level of convenience of use" as the product it is replacing (proposed §2.125(g)(3)(i) and (g)(4)(i));

- allow consideration of foreign post-marketing data which is supportive of US data (ILK, *Determinations of Continued Essentiality);*

- provide that a "post-marketing study" is not mandatory if other data are sufficient to substantiate the safety and efficacy of an alternative product (111.8, Specific Comment on the ANPRM Number 56);

- require that patients are "adequately served" by an alternative product (proposed §2.125(g)(3)(iv)); a multiple-dose dry powder inhaler, meet the essential use criteria listed in proposed §2.125(g)(3) in order to qualify as an acceptable alternative;

- remove the essential use designation for nasal inhalants.

SPH31

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